Maternal Hypertensive Pregnancy Disorders and Mental Disorders in Children

MATERNAL HYPERTENSIVE PREGNANCY DISORDERS AND MENTAL DISORDERS IN CHILDREN

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ABSTRACT

The associations of maternal hypertensive pregnancy disorders with offspring mental disorders remain unclear. We examined whether maternal hypertensive disorders and maximum blood pressure during pregnancy predict offspring childhood mental disorders, whether the associations are independent of maternal and paternal mental disorders and paternal hypertensive disorders, independent of or additive with maternal early pregnancy overweight/obesity and diabetes disorders, and/or mediated or moderated by preterm birth, small-for-gestational-age birth and/or neonatal intensive care unit admission. Our prospective study comprised 4743 mother-child dyads of Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction-study. Women were recruited to the study in early pregnancy at Finnish maternity hospitals. Children were born 2006─2010 and followed-up until 12/31/2016, to ages 6.4-10.8-years. Hypertensive pregnancy disorders were identified from medical records, Medical Birth Register and Care Register for Health Care. Systolic and diastolic blood pressure were measured at antenatal clinics and/or hospital visits. Mental disorder diagnoses were identified from Care Register for Health Care. Maternal gestational and chronic hypertension, preeclampsia and its severity increased offspring hazard of any childhood mental disorder. The associations of preeclampsia (Hazard Ratio=1.66;95% Confidence Interval=1.14-2.42) and severe preeclampsia (Hazard Ratio=2.01;95% Confidence Interval=1.08-3.73) were independent of all covariates. Maternal hypertensive and diabetes disorders and overweight/obesity also additively increased offspring hazard of mental disorders. Preterm and small-for-gestational-age births and neonatal intensive care unit admission partially mediated the effects of any and severe preeclampsia on offspring mental disorders. To conclude, maternal hypertensive pregnancy disorders carry adverse consequences for offspring mental health.

Key Words: Preeclampsia/Pregnancy, Prospective Cohort Study, Hypertension, Mental Disorder, Epidemiology

INTRODUCTION

Hypertensive pregnancy disorders, including chronic hypertension, gestational hypertension, preeclampsia and eclampsia, are common complicating 5-10% of pregnancies.[1-2] They are key risk factors for maternal mortality,[1-2] stillbirth,[1,3] preterm birth[1,3] and intrauterine growth restriction (IUGR),[3] and predict cardiovascular morbidity in the mother and her offspring.[1-4]

Increasing evidence suggests that the offspring risk is not confined to perinatal and cardiovascular health. Rather, maternal hypertensive pregnancy disorders also predict increased offspring risk of mental disorders, psychiatric symptoms and neurodevelopmental problems.[5–13] According to recent meta-analyses,[9,10,12] any maternal hypertensive pregnancy disorder, defined as chronic or gestational hypertension or preeclampsia, predicts 1.4-fold offspring odds of autism spectrum disorders (ASD) and 1.3-fold odds of attention-deficit-hyperactivity-disorder (ADHD), with preeclampsia predicting also up to 1.5-fold odds of ADHD, ASD and schizophrenia. However, although individual studies suggest significant associations of maternal hypertensive pregnancy disorders with offspring developmental delay and any mental, mood and anxiety disorders,[8,9,12,13] whether maternal hypertensive disorders predict also other offspring mental disorders than ASD, ADHD or schizophrenia remains quite unexplored.

Other important knowledge gaps also remain. Firstly, it remains largely unknown whether there are dose-response effects: whether offspring mental disorder risk increases with increasing severity of maternal preeclampsia or increasing blood pressure during pregnancy. In one study, severity of preeclampsia predicted increased offspring risks of ASD and developmental delay,[11] but another study found that preeclampsia severity did not predict ASD or eating disorders.[7] Secondly, although hypertensive pregnancy disorders associate with poorer maternal mental health,[14] familial confounding by maternal mental disorders or

paternal mental or hypertensive disorders are almost never accounted for in these studies. Thirdly, while maternal overweight, obesity and diabetes disorders often co-occur with hypertensive disorders,[3] and predict offspring mental disorders,[15] few studies with contradictory findings have assessed whether hypertensive pregnancy disorders associate with offspring mental disorders independently of or additively with these conditions.[5–8,11,16] Finally, although hypertensive pregnancy disorders are risk factors for preterm birth, IUGR and neonatal complications and illnesses,[1,3,17] which all constitute risks for mental disorders,[17-19] it remains unknown whether preterm birth, IUGR or neonatal health conditions mediate or moderate the effects of maternal hypertensive pregnancy disorders on offspring mental disorders.

Hence, to address these gaps in knowledge, we examined among 4743 mother-child dyads, whether maternal chronic and gestational hypertension and preeclampsia were associated with offspring childhood mental disorders, in a follow-up from birth to 6.4-10.8 years. We also studied whether the associations were dose-dependent by categorizing preeclampsia according to its severity and examining in a subsample of 1027 mother-child dyads associations with maternal maximum systolic (SBP) and diastolic (DBP) blood pressure during pregnancy. We further studied whether any associations were independent of maternal mental disorders and paternal mental and hypertensive disorders, independent of and/or additive with maternal early pregnancy overweight/obesity and diabetes disorders and/or mediated or moderated by preterm birth and/or small-for-gestational-age (SGA) birth, approximating IUGR, and/or neonatal intensive care unit (NICU) admission, approximating neonatal complications and illnesses.

METHODS

Because of the sensitive nature of the data collected for this study, study data cannot be made open access. Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) Study Board. Data requests may require further review by national register authorities and ethical committees.[20]

Our study cohort, PREDO, comprises 4777 women and their singleton children born alive in Finland 2006-2010. The cohort profile describes the study design.[20] The women were recruited to the study at their first ultrasound screen visit at 12-14 gestational weeks at ten study hospitals in Southern and Eastern Finland.

Of the 4777 mother-child dyads, 34 (0.7%) were excluded, since three women withdrew consent and 31 dyads lacked data on hypertensive and/or mental disorders. Hence, our study sample comprised 4743 mother-child dyads, 99.3% of the original cohort.

A subsample (n=1079) of this cohort was recruited based on known clinical risk factor status for preeclampsia and IUGR.[20] This enriched the sample in terms of preeclampsia incidence, which in Finland varies between 0.8% and 1.9%.[20,21] This subsample had thorough medical record data available, including blood pressure data during pregnancy for 1027 of the 1079 (95.2%; 4.8% with missing data) women.

All participating women signed informed consent, which enabled linkage of nationwide health register data using unique personal identification numbers assigned to all Finnish citizens and permanent residents since 1971. The PREDO study protocol was approved by ethical committees of Helsinki and Uusimaa Hospital District and study hospitals.

Maternal Hypertensive Disorders

Table S1 in Online Data Supplement (please see http://hyper.ahajournals.org) specifies our diagnostic classification of maternal hypertensive disorders, and provides the diagnostic criteria,[2,22] diagnostic codes and cumulative incidence of these disorders in our sample. We grouped hypertensive disorders into five groups: hypertensive disorders only before current pregnancy (hypertensive disorders in previous pregnancies or chronic hypertension only before current pregnancy), and unspecified hypertension, chronic hypertension, gestational hypertension and preeclampsia in current pregnancy. Women with eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) or preeclampsia superimposed on chronic hypertension were also included in the preeclampsia group. Preeclampsia was further categorized into mild/moderate and severe. Normotensive women with no hypertensive disorders before or during current pregnancy constituted the reference group (Table S1).

Hypertensive disorder diagnoses were identified from medical records and two nationwide registers; Finnish Care Register for Health Care (HILMO) and Medical Birth Register (MBR). HILMO carries all diagnoses of all inpatient (since 1969) and open-ward hospitalizations and outpatient treatments in public specialized-care (since 1998) in Finland. MBR includes diagnoses from hospital treatments during pregnancy or childbirth since 1987. Both registers are validated research tools.[23,24] In Finland, International Classification of Diseases, Eighth Revision (ICD-8) was used until 1986, ICD-9 in 1987-1995, and ICD-10 has been used since 1996.

For women recruited based on known clinical risk factor status, an expert jury comprising two physicians and a nurse verified the diagnoses. The register-based diagnoses showed

substantial concordance with the clinician-verified diagnoses (Table S2; kappa=0.66, Gwet's AC1 coefficient=0.79).

Blood Pressure during Pregnancy

We identified maximum SBP and DBP (mmHg) values during pregnancy from medical records. The records comprise measurements conducted at antenatal clinic visits (11-15 visits during pregnancy in Finland) and/or hospital visits for suspected hypertensive disorders. Most often, public health nurses or midwives conducted the blood pressure measurements according to Finnish Current Care Guidelines (https://www.kaypahoito.fi/en): after a five minute rest, from the upper arm and in seated position. If blood pressure values were very high, the measurements were repeated and the lower value was coded into the medical records to avoid white coat hypertension effects.

Offspring Childhood Mental Disorders

Mental disorder diagnoses were identified from HILMO with ICD-10 codes F00-F99 from birth until 12/31/2016. Table S3 shows the diagnostic codes and cumulative incidences of specific mental disorders and medians and interquartile ranges of age at first diagnosis. To increase statistical power, we focused on any childhood mental disorder (ICD-10:F00-F99) and psychological development disorders (ICD-10:F80-F89) and behavioral and emotional disorders (ICD-10:F90-F98) as outcomes, since they were the most frequent.

Covariates, additive factors, mediators and moderators

As covariates, we examined maternal smoking (did not smoke/quit during 1st trimester/smoked throughout) and alcohol use (yes/no) during pregnancy, parity (primiparous/other), age at delivery (years), education level (primary or secondary/lower tertiary/upper tertiary) and lifetime diagnosis of maternal and paternal any mental disorder (yes/no; ICD-8 and ICD-9:290-315; ICD-10:F00-F99) and paternal hypertensive disorders (yes/no; ICD-8 and ICD-9:40; ICD-10:I1) and offspring sex and birth year. We extracted data on maternal smoking, parity and age and offspring sex and birth year from MBR and maternal alcohol use and education from early pregnancy self-reports. Lifetime diagnosis of maternal and paternal any mental disorder and paternal hypertensive disorders were identified from HILMO until 12/31/2016. We identified fathers from population register as male spouses married to the mother at childbirth.

As covariates and additive factors, we examined maternal body mass index (BMI) in early pregnancy and diabetes disorders, which we derived from medical records, MBR and HILMO. For the sample recruited based on known risk factor status, also diabetes diagnoses were jury-verified. Maternal weight and height were measured at first antenatal clinic visits at a mean 8.6 (standard deviation=1.5) gestational weeks. BMI was calculated as weight (kilograms)/height (meters)^2, and categorized into underweight (BMI<18.5), normal weight (BMI=18.5-24.9), overweight (BMI=25-29.9) and obese (BMI≥30). Type 1 diabetes (ICD-9:2500A-2509A; ICD-10:E10), type 2 diabetes (ICD-9:2500B-2509B; ICD-10:E11) and any diabetes in current pregnancy (ICD-10:O24) were combined into one category and any diabetes in previous pregnancy (ICD-9:6480A, 6488A; ICD-10:O24) into another.

As mediators and moderators, we examined preterm birth (<37+0 weeks), SGA birth (birth weight<-2 standard deviation units adjusted for sex and gestational age according to national growth curves[25]) and NICU admission (yes/no), which we extracted from MBR.

Statistics

With Cox Regression, we estimated the associations of maternal hypertensive disorders, preeclampsia severity and maximum blood pressure during pregnancy with any childhood mental disorder, psychological development and behavioral and emotional disorders in the offspring. In the analyses of hypertensive disorders, normotensive women were the reference group.

To study if associations of maternal hypertensive disorders with offspring childhood mental disorders were independent of maternal mental disorders, overweight/obesity and diabetes disorders, and paternal mental and hypertensive disorders, we added them as covariates into the Cox models.

We then examined with Cox models the additive effects of maternal hypertensive disorders, overweight/obesity and diabetes disorders on offspring childhood mental disorders. For this purpose, we summed up if the mother had any hypertensive pregnancy disorder (1=yes; 0=no), overweight/obesity (1=yes; 0=no) or any diabetes disorder (1=yes; 0=no). The number of adverse pregnancy conditions varied from 0 (none of these conditions) to 3 (all three conditions). We excluded women who were underweight or had hypertension only before current pregnancy or diabetes only in previous pregnancy from these additive effect analyses.

All these analyses were also adjusted for all maternal, paternal and offspring covariates (see Table 1 footnotes). Standard deviations, interquartile ranges and 95% confidence intervals

were used as measures of variance. The statistical analyses were conducted with IBM SPSS Statistics 24.0-25.0, SAS 9.3 and RStudio-software.

In sensitivity analyses, we examined whether excluding women with HILMO or MBR diagnosis of coronary heart disease (ICD-9:410-414; ICD-10:I20-I25, n=4) or stroke (ICD-9:430-434, 436-438; ICD-10:I6, n=7) before childbirth or genitourinary infections in current pregnancy (ICD-10:O23, n=23) affected our findings. No women had chronic kidney disease (ICD-9:585; ICD-10:N18).

Next, we assessed whether preterm birth, SGA birth and/or NICU admission mediated the associations between maternal hypertensive disorders and offspring childhood mental disorders, using logistic regressions and Sobel Tests. Mediation was tested only for maternal hypertensive disorders independently associated with offspring mental disorders and only if the mediator associated with the predictor and outcome variables. To study moderation, we examined interaction effects of preterm and SGA births and NICU admission with maternal hypertensive disorders on offspring childhood mental disorders.

RESULTS

Table S4 shows the sample characteristics and associations of covariates, additive factors, mediators and moderators with maternal hypertensive disorders. In our sample, 200 women had chronic hypertension, 4 unspecified hypertension, 263 gestational hypertension and 209 preeclampsia during current pregnancy and 333 hypertensive disorders only before current pregnancy.

Table S3 shows that 412 (8.7%) offspring were diagnosed with any childhood mental disorder during the follow-up. Of them, 256 had psychological development and 200 behavioral and emotional disorders.

Maternal and paternal mental disorders, maternal smoking during pregnancy, early pregnancy overweight and obesity, diabetes disorders and lower education and offspring's male sex, preterm and SGA birth and NICU admission predicted increased offspring hazard of any childhood mental disorder (Table S5). Maternal age, parity and alcohol use during pregnancy and paternal hypertensive disorders did not predict offspring childhood mental disorders.

Maternal Hypertensive Disorders and Offspring Childhood Mental Disorders

Table 1 shows that maternal chronic hypertension, gestational hypertension and preeclampsia in current pregnancy each predicted increased hazard of any childhood mental disorder in the offspring. Preeclampsia also predicted offspring psychological development and behavioral and emotional disorders, while chronic and gestational hypertension were associated with offspring psychological development disorders (Table 1). All associations were independent of maternal mental disorders, paternal mental and hypertensive disorders, maternal age, parity, smoking, alcohol use and education and offspring covariates. However, only the effects of maternal preeclampsia were independent of maternal overweight/obesity and

diabetes disorders. Hypertensive disorders only before current pregnancy and unspecified hypertension during current pregnancy did not predict offspring childhood mental disorders.

Severity of Preeclampsia and Offspring Childhood Mental Disorders

Both severe and mild/moderate preeclampsia in current pregnancy predicted increased offspring hazard of any childhood mental, psychological development and behavioral and emotional disorders (Table 1). These associations were independent of maternal and paternal mental disorders, paternal hypertensive disorders, maternal age, smoking, alcohol use, parity and education and offspring covariates. When we adjusted for maternal overweight/obesity and diabetes disorders, only severe preeclampsia remained significantly associated with any childhood mental and behavioral and emotional disorders. Figure 1 displays these associations and shows that offspring hazard of any childhood mental, psychological development and behavioral and emotional disorders increased linearly according to preeclampsia severity.

Maternal Blood Pressure during Pregnancy and Offspring Childhood Mental Disorders

Higher maternal maximum SBP during pregnancy was associated with increased offspring hazard of any childhood mental and psychological development disorders, but these associations were not independent of covariates (Table 1). Maternal maximum DBP during pregnancy did not predict offspring mental disorders.

Additive Effects of Maternal Adverse Pregnancy Conditions on Offspring Childhood Mental Disorders

Maternal hypertensive disorders, overweight/obesity and diabetes disorders had additive effects increasing offspring hazard of any childhood mental, psychological development and behavioral and emotional disorders, independently of maternal and paternal mental disorders, paternal hypertensive disorders and other covariates (Figure 2, Table 1).

Sensitivity Analyses

Table S6 shows that the effects of maternal hypertensive pregnancy disorders and preeclampsia severity and additive effects of adverse pregnancy conditions on offspring childhood mental disorders remained unchanged when we excluded women with coronary heart disease and stroke diagnosed by childbirth and genitourinary infections during pregnancy.

Mediation and Moderation via Preterm and SGA Births and NICU admission

Preterm birth, SGA birth and NICU admission each partially mediated the effects of preeclampsia and severe preeclampsia on any childhood mental disorder in the offspring (Figure 3). SGA birth and NICU admission partially mediated the effects of preeclampsia on offspring psychological development disorders and preterm birth and NICU admission of any and severe preeclampsia on offspring behavioral and emotional disorders (Figure S1). Hypertensive pregnancy disorders did not interact with preterm or SGA births or NICU admission in predicting offspring childhood mental disorders (all p-values≥.09).

DISCUSSION

We show here that maternal preeclampsia and its severity increase the hazard of any childhood mental disorder, and specifically psychological development and behavioral and emotional disorders in the offspring from birth to 6.4-10.8 years. We also show that these associations are not explained by maternal mental disorders, age, substance use, parity, education, overweight/obesity or diabetes disorders or paternal mental or hypertensive disorders. While chronic and gestational hypertension also associate with any childhood mental and psychological development disorders in the offspring, these associations do not survive adjustments for maternal overweight/obesity and diabetes disorders. However, maternal hypertensive disorders, overweight/obesity and diabetes disorders in pregnancy additively increase the cumulative incidence of childhood mental disorders from 6.6% to 22.2% in offspring exposed to none compared to all these three adverse maternal conditions. Finally, the effects of preeclampsia and severe preeclampsia on child mental disorders are partially mediated by preterm and SGA births and NICU admission.

Our findings correspond with recent meta-analyses, which, however, were restricted to a few neuropsychiatric disorders, namely ASD, ADHD and schizophrenia.[9,10,12] We are among the first to show that the effects of maternal hypertensive pregnancy disorders are not limited to these disorders, but extend to any childhood mental, psychological development and behavioral and emotional disorders in the offspring. The observed effect sizes, 1.7-1.9-fold increased hazards of any childhood mental disorder, are slightly higher than the previously reported 1.3-1.5-fold risks of ASD, ADHD and schizophrenia. The hazards are also slightly higher than those related to preterm and SGA births and NICU admission in our sample.

This is among the first studies to show that maternal hypertensive pregnancy disorders predict offspring childhood mental disorders independently of maternal and paternal mental

disorders and paternal hypertensive disorders, suggesting that hereditary susceptibility does not explain the associations. We are also among the first to show that preeclampsia and its severity show associations with offspring mental disorders which are independent of maternal overweight/obesity and diabetes disorders. These findings correspond with the few available studies which showed similar independent associations of any hypertensive pregnancy disorder with child ASD and developmental delay,[5] preeclampsia with child ADHD[8] and ASD,[11] and preeclampsia or gestational hypertension with adolescent anxiety disorders[6] but contrast those of another study which showed no associations of preeclampsia with child ASD when controlling for maternal overweight/obesity.[16] Furthermore, the severity of preeclampsia findings support previous ones on child ASD and developmental delay,[11] although findings are inconsistent.[7]

However, the main effects of chronic and gestational hypertension on offspring mental disorders were non-significant after adjustment for maternal diabetes and overweight/obesity. This suggests shared biological pathways underlying the effects of these maternal conditions on offspring mental disorders, for example neuronal brain network hyperexcitability in children exposed to maternal cardiovascular dysfunction.[26]

Maternal hypertensive pregnancy disorders, overweight/obesity and diabetes disorders also had additive effects on offspring mental disorders. Previously, among all children born in Finland 2004-2014, maternal severe obesity and type 1 diabetes had additive effects on several childhood and adolescence mental disorders.[15] Our novel findings suggested that such effects are not restricted to severe obesity and type 1 diabetes but extend across the range of maternal overweight/obesity, hypertensive and diabetes disorders, suggesting that besides cardiovascular dysfunction, maternal metabolic alterations may also affect neurodevelopment.

We also show that preterm birth, SGA birth and NICU admission partially mediate the effects of preeclampsia and severe preeclampsia on offspring childhood mental disorders. Correspondingly, low birth weight was recently shown to partially mediate the effects of hypertensive pregnancy disorders on offspring childhood depression.[13] Children born preterm and/or SGA have altered structural brain development, contributing to their increased mental disorder risk.[17] These alterations may also be among the biological pathways underpinning the offspring mental disorder risk associated with maternal preeclampsia.

Such pathways may also include alterations in placental, immune system and hypothalamic-pituitary-adrenal (HPA) axis functioning, shared genetic background and/or epigenetic changes. Preeclampsia is often characterized by placental insufficiency,[21,27] which also associates with offspring mental disorders.[11] Previous studies show altered HPA axis and immune system functioning among women with hypertensive pregnancy disorders[28,29] and associations of maternal HPA axis activity and inflammation during pregnancy with offspring mental disorders.[30,31] Evidence also suggests partially shared genetics for hypertension and mental disorders,[32] and DNA methylation changes in offspring exposed to maternal hypertensive pregnancy disorders[33] and patients with mental disorders.[34]

While no universally efficient methods have been developed, international guidelines suggest several promising prevention and treatment strategies for hypertensive pregnancy disorders and particularly preeclampsia.[2,27] These include aspirin, magnesium sulfate, and antihypertensive drug treatment, exercise and clinical monitoring of IUGR and preeclampsia risks.[2,27] Our findings suggest that such interventions may benefit both maternal and offspring well-being.

The strengths of our study include its prospective design, large sample size, validated register data on hypertensive and mental disorders and minimal, 0.7% follow-up attrition. We

assessed several important covariates, including maternal mental disorders, overweight/obesity and diabetes disorders, and paternal mental and hypertensive disorders. Study limitations include the observational design, which precludes causal inferences. We had maternal blood pressure data only for a subsample, and the associations of maternal blood pressure with offspring mental disorders were less consistent than those of hypertensive pregnancy disorders, possibly due to limited statistical power. Since this subsample was a high-risk sample for preeclampsia and IUGR, blood pressure levels were high, which limits generalizability. The electronic medical records contained systematic data only on maximum blood pressure values during pregnancy, not values from all measurements. This also contributed to the high blood pressure levels, further limiting variance, statistical power and generalizability. Larger, population-wide studies using more reliable, average blood pressure values across pregnancy should confirm if our findings extend to all pregnant women and their offspring. Since our sample was mostly Caucasian in a high-income country with universal health care, generalizability to other populations is also limited. While we identified all offspring mental disorders until ages 6.4-10.8 years, some disorders, including schizophrenia, mood and substance use disorders usually have their onset later, in adolescence or adulthood. Hence, our findings generalize best to any childhood mental disorder. Furthermore, recent guidelines introduce changes to the diagnostic classification of preeclampsia.[27,29] Proteinuria is no longer a necessary criterion. Rather, preeclampsia is now diagnosed as de novo hypertension after 20 gestational weeks together with proteinuria *and/or* evidence of maternal acute kidney injury, liver dysfunction, neurological features, hemolysis, thrombocytopenia, or IUGR.[27] The guidelines also suggest removal of preeclampsia severity assessment in clinical practice, although acknowledging its benefits for research purposes.[27,29] Indeed, from the etiological perspective of childhood mental disorders, this information may be important.

PERSPECTIVES

Maternal hypertensive pregnancy disorders, especially preeclampsia and its severity, predict increased offspring hazard of any childhood mental disorder. These effects are independent of parental mental disorders, paternal hypertensive disorders and several other covariates, independent of and additive with maternal overweight/obesity and diabetes disorders, and partially mediated by preterm and SGA births and NICU admission. Our findings highlight the adverse intergenerational consequences of maternal preeclampsia on offspring mental health.

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NOVELTY AND SIGNIFICANCE:

1) What Is New? We were the first to show that preeclampsia predicts increased offspring hazard of any childhood mental disorder independently of parental mental disorders, maternal overweight/obesity and diabetes disorders and paternal hypertensive disorders.

2) What Is Relevant? Our findings highlight that hypertensive pregnancy disorders carry adverse consequences not only for maternal and offspring cardiovascular health, but also for offspring mental health.

Summary: In our prospective study among 4743 mother-child dyads, hypertensive pregnancy disorders, especially preeclampsia and its severity, predicted offspring childhood mental disorders from birth until ages 6-10 years.

FIGURE LEGENDS

Figure 1. Severity of preeclampsia and offspring childhood mental disorders.

Cumulative incidences and median ages (interquartile range) at first diagnosis of any childhood mental (Panel A), psychological development (Panel B) and behavioral and emotional disorders (Panel C) in the offspring of normotensive mothers, mothers with mild/moderate preeclampsia and severe preeclampsia, from Kaplan-Meier analyses. P-values refer to linear trends from Cox models where preeclampsia severity (0=normotension; 1=mild/moderate preeclampsia; 2=severe preeclampsia) predicted offspring childhood mental disorders, stratifying for offspring sex and adjusting for offspring birth year (model 1), maternal age, parity, education, smoking and alcohol use during pregnancy (model 2), maternal and paternal mental disorders and paternal hypertensive disorders (model 3) and maternal overweight/obesity and diabetes disorders (model 4).

Figure 2. Additive effects of maternal adverse pregnancy conditions on offspring childhood mental disorders.

Cumulative incidences and median ages (interquartile range) at first diagnosis of any mental (Panel A), psychological development (Panel B) and behavioral and emotional disorders (Panel C) in the offspring born to mothers with none, one, two or three maternal adverse pregnancy conditions (any hypertensive disorder, overweight/obesity, any diabetes disorder), from Kaplan-Meier analyses. P-values from Cox models examining the number of adverse pregnancy conditions as a linear predictor of offspring mental disorders, stratifying and adjusting for the model 1-3 covariates listed in the legend of Figure 1.

Figure 3. Preterm birth, small-for-gestational-age birth and neonatal intensive care unit admission partially mediate the effects of preeclampsia on offspring childhood mental disorders. The figures show the results of Sobel test mediation analyses of preterm birth (Panels A-B), small-for-gestational-age birth (Panels C-D) and neonatal intensive care unit admission (Panels E-F) as mediators of the effects of preeclampsia and severe preeclampsia on any childhood mental disorder in the offspring. Standardized regression coefficients (β) and confidence intervals (CI) from unadjusted Sobel tests and logistic regressions.

Table 1. Maternal Hypertensive Disorders, Blood Pressure and Adverse Pregnancy Conditions and Offspring Hazard of Mental Disorders.

	Offspring Mental Disorders					
	Any Childhood Mental Disorder		Psychological Development Disorders		Behavioral and Emotional Disorders	
	HR(95 % CI)*	P	HR(95% CI)*	p	HR(95% CI)*	p
Maternal Hypertensive Disorder Only Before Current Pregnancy vs. Normotension						
Model 1	0.76(0.49-1.18)	.22	0.85(0.49-1.46)	.55	0.50(0.23-1.07)	.07
Model 2	0.80(0.51-1.26)	.34	0.89(0.51-1.55)	.68	0.56(0.26-1.22)	.15
Model 3	0.79(0.50-1.23)	.30	0.87(0.50-1.52)	.62	0.55(0.25-1.18)	.12
Model 4	0.75(0.48-1.18)	.21	0.83(0.47-1.45)	.51	0.52(0.24-1.14)	.10
Maternal Unspecified Hypertension in Current Pregnancy vs. Normotension						
Model 1	3.40(0.48-24.23)	.22	5.72(0.80-40.85)	.08	0(NA*)	.96
Model 2	3.38(0.47-24.17)	.22	5.63(0.78-40.39)	.09	0(NA*)	.98
Model 3	3.89(0.54-27.80)	.18	6.63(0.92-47.61)	.06	0(NA*)	.98
Model 4	3.28(0.46-23.53)	.24	5.54(0.77-39.97)	.09	0(NA*)	.98
Maternal Chronic Hypertension in Current Pregnancy vs. Normotension						
Model 1	1.57(1.05-2.34)	.03	1.92(1.19-3.09)	.01	1.43(0.79-2.58)	.24
Model 2	1.57(1.04-2.37)	.03	1.89(1.16-3.08)	.01	1.54(0.84-2.81)	.16
Model 3	1.60(1.06-2.42)	.02	1.95(1.20-3.19)	.01	1.60(0.87-2.92)	.13
Model 4	1.24(0.81-1.90)	.32	1.48(0.89-2.45)	.13	1.18(0.64-2.21)	.59
Maternal Gestational Hypertension in Current Pregnancy vs. Normotension						
Model 1	1.54(1.07-2.21)	.02	1.73(1.11-2.69)	.02	1.21(0.69-2.14)	.50
Model 2	1.45(1.01-2.08)	.05	1.60(1.02-2.51)	.04	1.17(0.66-2.06)	.60
Model 3	1.47(1.02-2.12)	.04	1.64(1.05-2.57)	.03	1.19(0.67-2.10)	.56
Model 4	1.28(0.88-1.85)	.20	1.41(0.89-2.22)	.14	0.98(0.55-1.76)	.95
Maternal Preeclampsia in Current Pregnancy vs. Normotension						
Model 1	1.89(1.31-2.74)	.001	2.16(1.37-3.39)	.001	2.21(1.35-3.61)	.002
Model 2	1.93(1.33-2.80)	.001	2.23(1.41-3.51)	.001	2.26(1.38-3.70)	.001
Model 3	1.92(1.33-2.79)	.001	2.21(1.40-3.48)	.001	2.29(1.40-3.75)	.001
Model 4	1.66(1.14-2.42)	.01	1.87(1.18-2.96)	.01	1.96(1.19-3.23)	.01
Maternal Mild/Moderate Preeclampsia in Current Pregnancy vs. Normotension						
Model 1	1.64(0.99-2.72)	.05	1.88(1.02-3.45)	.04	2.08(1.10-3.95)	.03
Model 2	1.65(1.00-2.74)	.05	1.91(1.04-3.53)	.04	2.10(1.10-3.99)	.02
Model 3	1.67(1.01-2.76)	.05	1.94(1.05-3.57)	.03	2.15(1.13-4.09)	.02
Model 4	1.40(0.84-2.34)	.19	1.60(0.86-2.97)	.14	1.80(0.94-3.45)	.08
Maternal Severe Preeclampsia in Current Pregnancy vs. Normotension						
Model 1	2.25(1.23-4.13)	.01	2.40(1.12-5.16)	.02	2.96(1.38-6.37)	.01
Model 2	2.42(1.31-4.45)	.005	2.69(1.25-5.80)	.01	3.24(1.50-7.02)	.003
Model 3	2.31(1.25-4.26)	.01	2.54(1.18-5.50)	.02	3.12(1.44-6.77)	.004
Model 4	2.01(1.08-3.73)	.03	2.15(0.99-4.70)	.05	2.76(1.26-6.06)	.01
Maternal Systolic Blood Pressure during Current Pregnancy†						
Model 1	1.21(1.02-1.45)	.03	1.30(1.04-1.61)	.02	1.19(0.93-1.53)	.17
Model 2	1.16(0.97-1.38)	.11	1.24(0.99-1.55)	.06	1.13(0.88-1.46)	.35
Model 3	1.18(0.98-1.41)	.07	1.27(1.01-1.59)	.03	1.14(0.88-1.48)	.31
Model 4	1.11(0.92-1.34)	.29	1.17(0.92-1.49)	.21	1.06(0.81-1.40)	.66

Maternal Diastolic Blood Pressure during Current Pregnancy†						
Model 1	1.15(0.96-1.38)	.13	1.18(0.95-1.49)	.14	1.07(0.83-1.39)	.59
Model 2	1.12(0.93-1.34)	.24	1.15(0.91-1.45)	.23	1.03(0.79-1.35)	.82
Model 3	1.13(0.94-1.35)	.20	1.17(0.93-1.46)	.19	1.05(0.80-1.37)	.74
Model 4	1.05(0.87-1.28)	.61	1.05(0.82-1.35)	.67	0.96(0.72-1.27)	.77
Number of Maternal Adverse Pregnancy Conditions‡						
1 vs. 0						
Model 1	1.48(1.17-1.89)	.001	1.48(1.09-2.02)	.01	1.42(1.00-2.02)	.05
Model 2	1.43(1.12-1.82)	.004	1.42(1.04-1.94)	.03	1.39(0.98-1.98)	.06
Model 3	1.42(1.11-1.81)	.005	1.42(1.04-1.94)	.03	1.37(0.97-1.95)	.08
2 vs. 0						
Model 1	2.06(1.53-2.75)	<.001	2.57(1.81-3.64)	<.001	2.02(1.33-3.08)	.001
Model 2	1.95(1.45-2.63)	<.001	2.43(1.70-3.46)	<.001	2.03(1.33-3.11)	.001
Model 3	1.90(1.41-2.55)	<.001	2.35(1.64-3.35)	<.001	1.95(1.27-2.99)	.002
3 vs. 0						
Model 1	3.28(2.25-4.79)	<.001	3.26(1.99-5.32)	<.001	3.87(2.32-6.45)	<.001
Model 2	2.99(2.03-4.41)	<.001	2.93(1.77-4.84)	<.001	3.86(2.28-6.54)	<.001
Model 3	2.94(1.99-4.34)	<.001	2.94(1.78-4.88)	<.001	3.68(2.16-6.25)	<.001

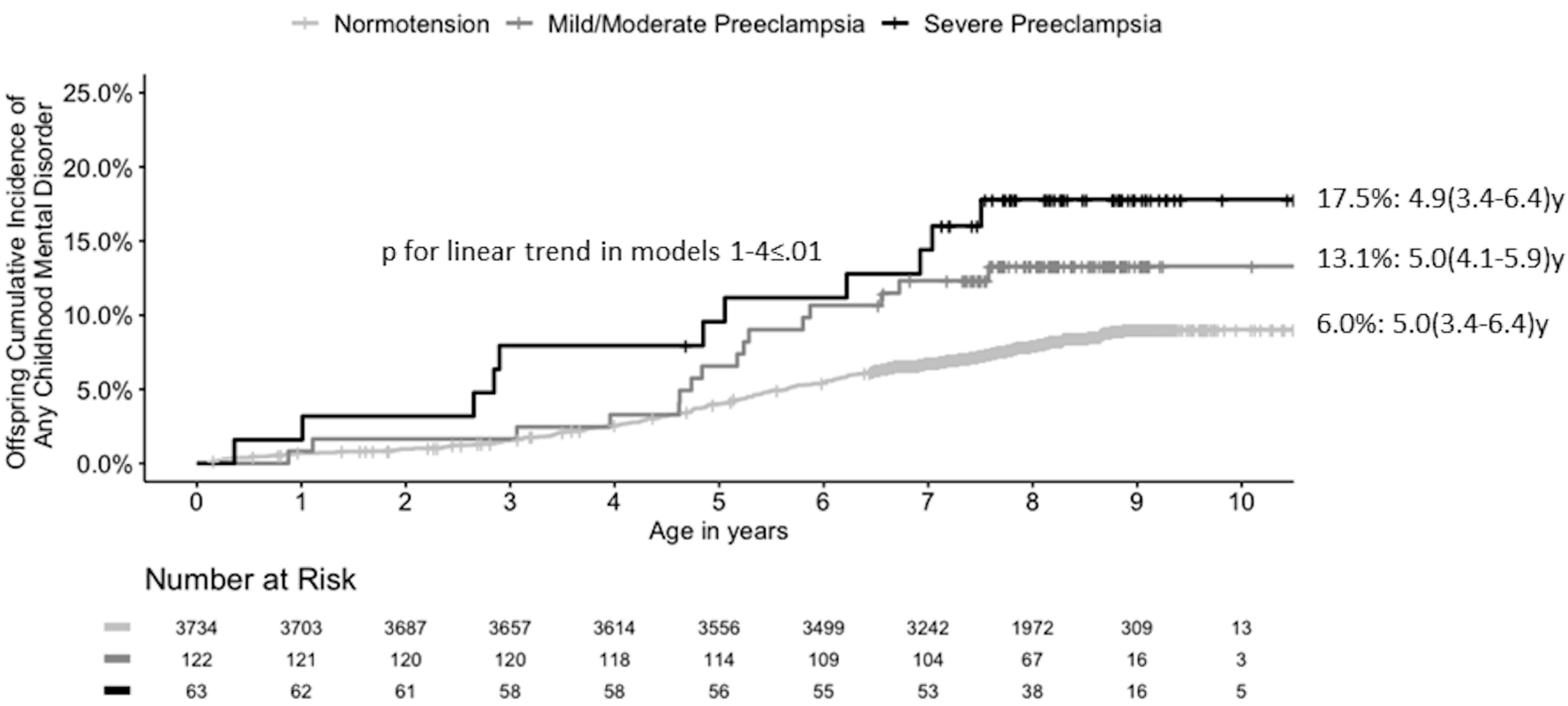
Model 1 is adjusted for offspring birth year and stratified for offspring sex and Model 2 also for maternal education, parity, age, alcohol use and smoking during pregnancy. Model 3 is adjusted further for maternal and paternal mental disorders and paternal hypertensive disorders and Model 4 for maternal early pregnancy overweight/obesity and diabetes disorders. Participants with missing values on categorical covariates are coded into own groups.

*HR=Hazard Ratio: CI=Confidence Interval: NA=Not Available.

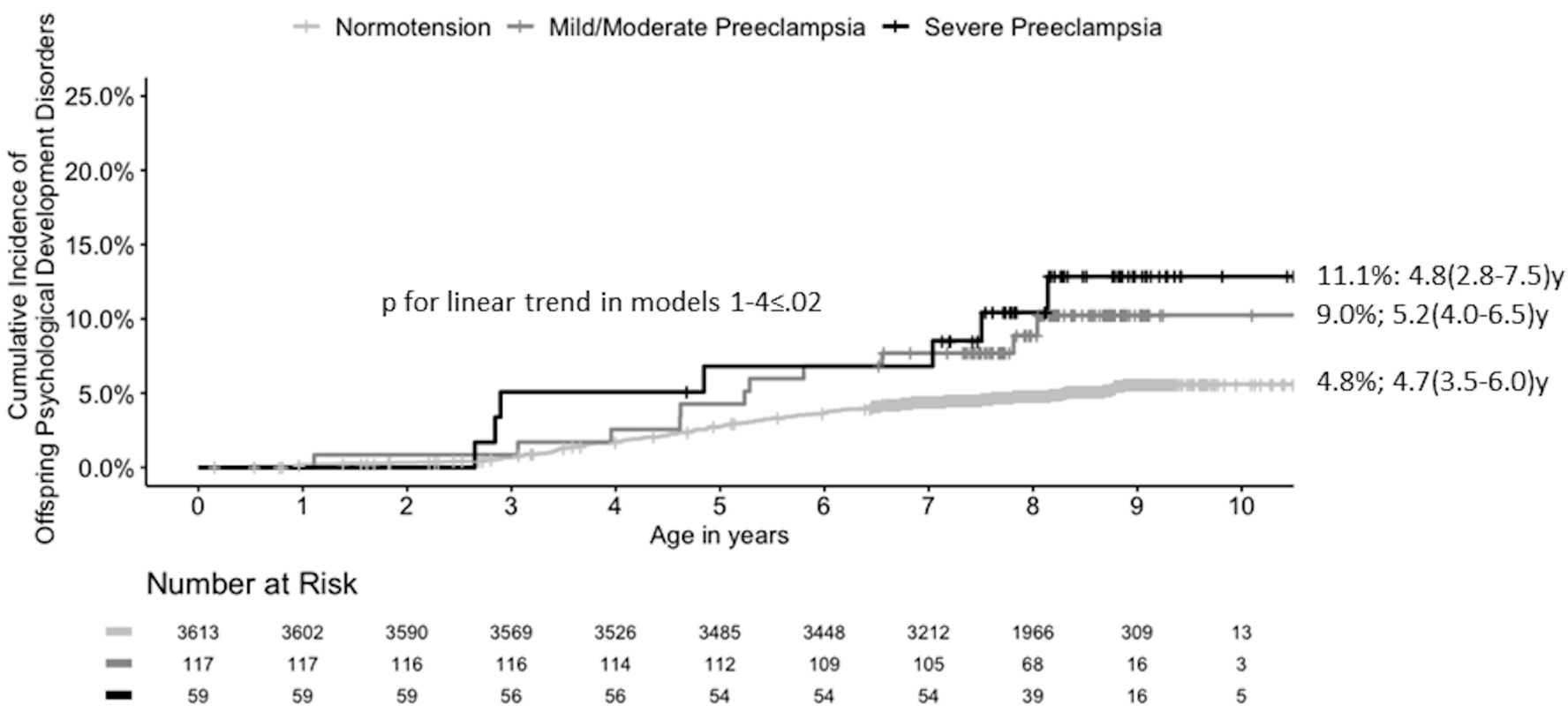
†Systolic blood pressure values are natural logarithm transformed to obtain normality. Diastolic and systolic blood pressure are expressed in standard deviation units.

‡Adverse pregnancy conditions are defined as overweight/obesity, diabetes and hypertensive disorders in current pregnancy. Normal weight, normotensive women with no diabetes disorders are the reference group. Women who were underweight, had diabetes only in previous pregnancy or hypertensive disorders only before current pregnancy are excluded from the additive effect analyses.

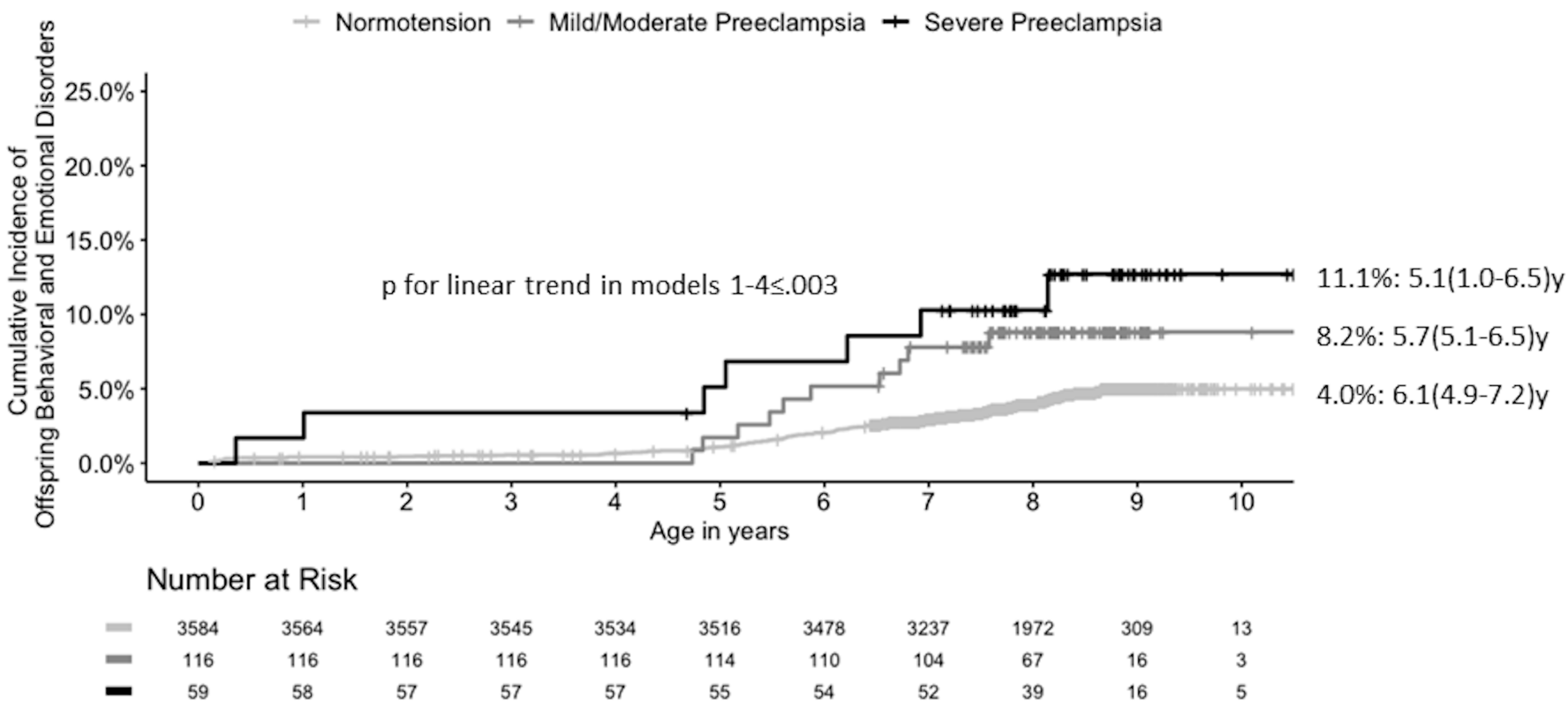
A


Normotension
Mild/Moderate Preeclampsia
Severe Preeclampsia
Offspring Cumulative Incidence of Any Childhood Mental Disorder
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
p for linear trend in models 1-4≤.01
17.5%: 4.9(3.4-6.4)y
13.1%: 5.0(4.1-5.9)y
6.0%: 5.0(3.4-6.4)y
0 1 2 3 4 5 6 7 8 9 10
Age in years
Number at Risk
3734 3703 3687 3657 3614 3556 3499 3242 1972 309 13
122 121 120 120 118 114 109 104 67 16 3
63 62 61 58 58 56 55 53 38 16 5

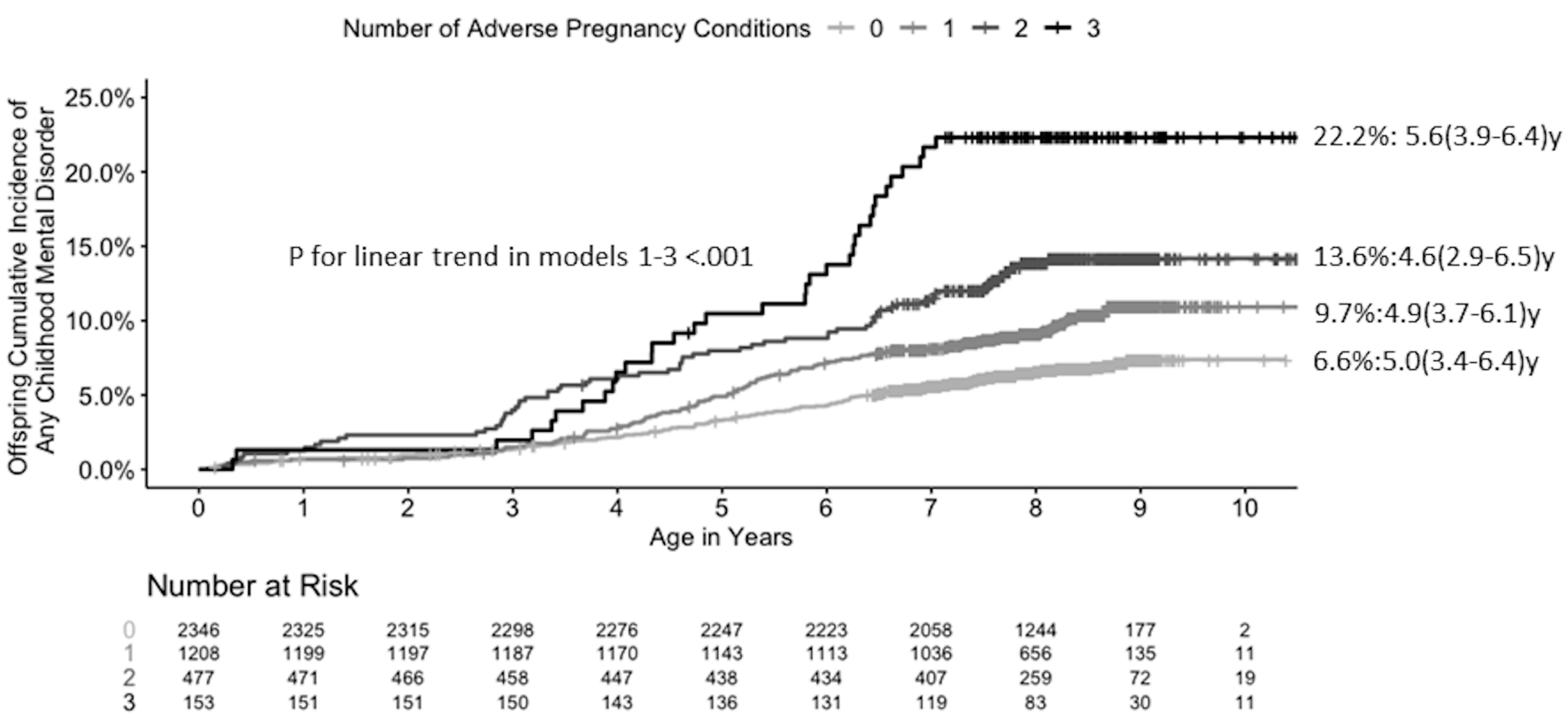
B


Normotension
Mild/Moderate Preeclampsia
Severe Preeclampsia
Cumulative Incidence of Offspring Psychological Development Disorders
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
p for linear trend in models 1-4≤.02
11.1%: 4.8(2.8-7.5)y
9.0%; 5.2(4.0-6.5)y
4.8%; 4.7(3.5-6.0)y
0 1 2 3 4 5 6 7 8 9 10
Age in years
Number at Risk
3613 3602 3590 3569 3526 3485 3448 3212 1966 309 13
117 117 116 116 114 112 109 105 68 16 3
59 59 59 56 56 54 54 54 39 16 5

C


Normotension
Mild/Moderate Preeclampsia
Severe Preeclampsia
Cumulative Incidence of Offspring Behavioral and Emotional Disorders
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
p for linear trend in models 1-4≤.003
11.1%: 5.1(1.0-6.5)y
8.2%: 5.7(5.1-6.5)y
4.0%: 6.1(4.9-7.2)y
0 1 2 3 4 5 6 7 8 9 10
Age in years
Number at Risk
3584 3564 3557 3545 3534 3516 3478 3237 1972 309 13
116 116 116 116 116 114 110 104 67 16 3
59 58 57 57 57 55 54 52 39 16 5

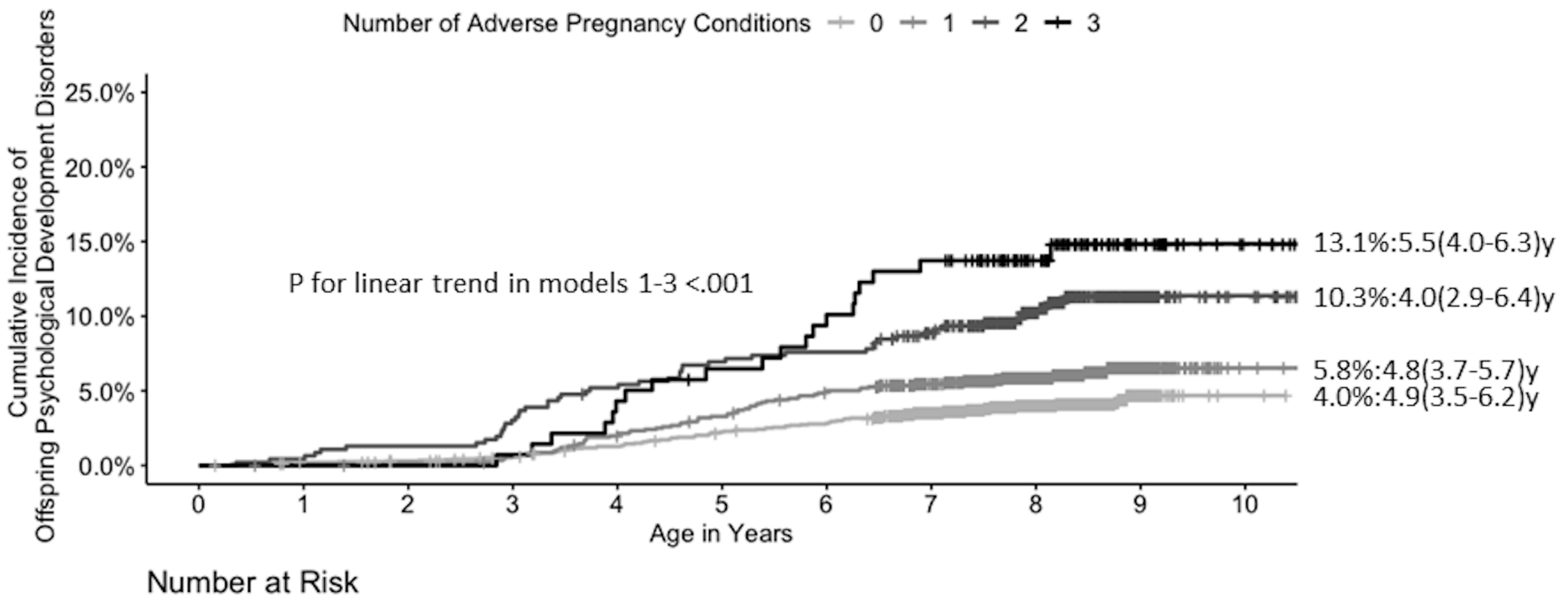
A.



Number at Risk

0	2346	2325	2315	2298	2276	2247	2223	2058	1244	177	2
1	1208	1199	1197	1187	1170	1143	1113	1036	656	135	11
2	477	471	466	458	447	438	434	407	259	72	19
3	153	151	151	150	143	136	131	119	83	30	11

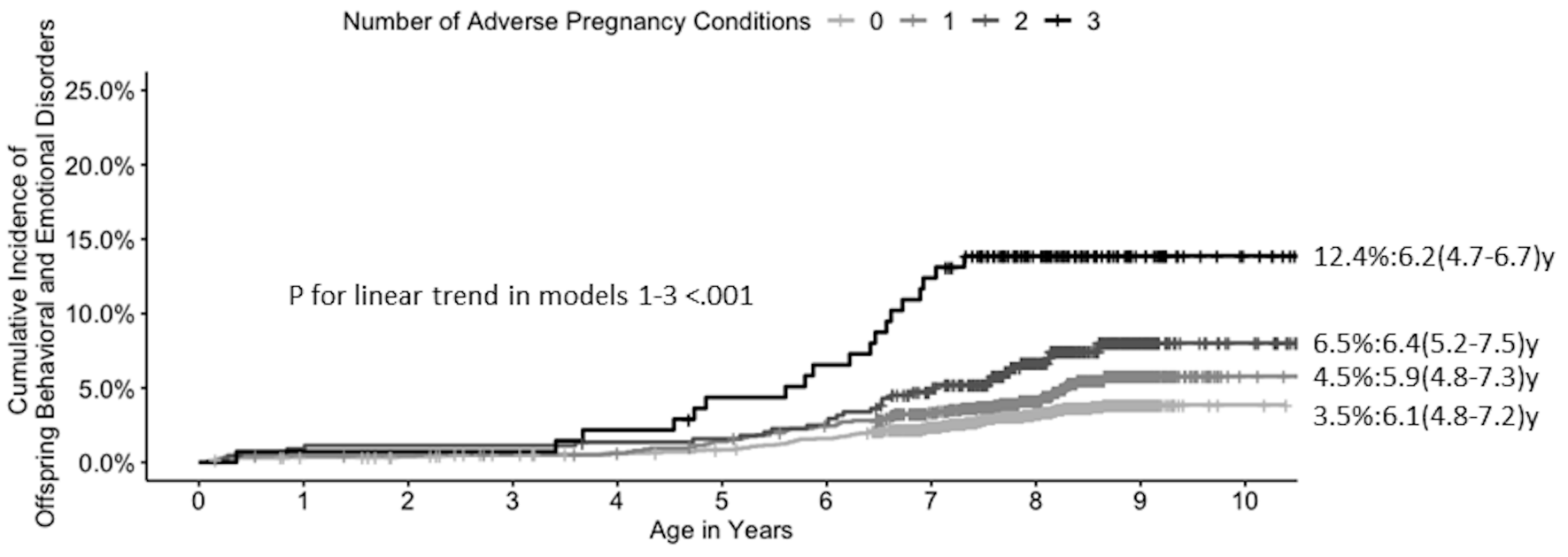
B.



Number at Risk

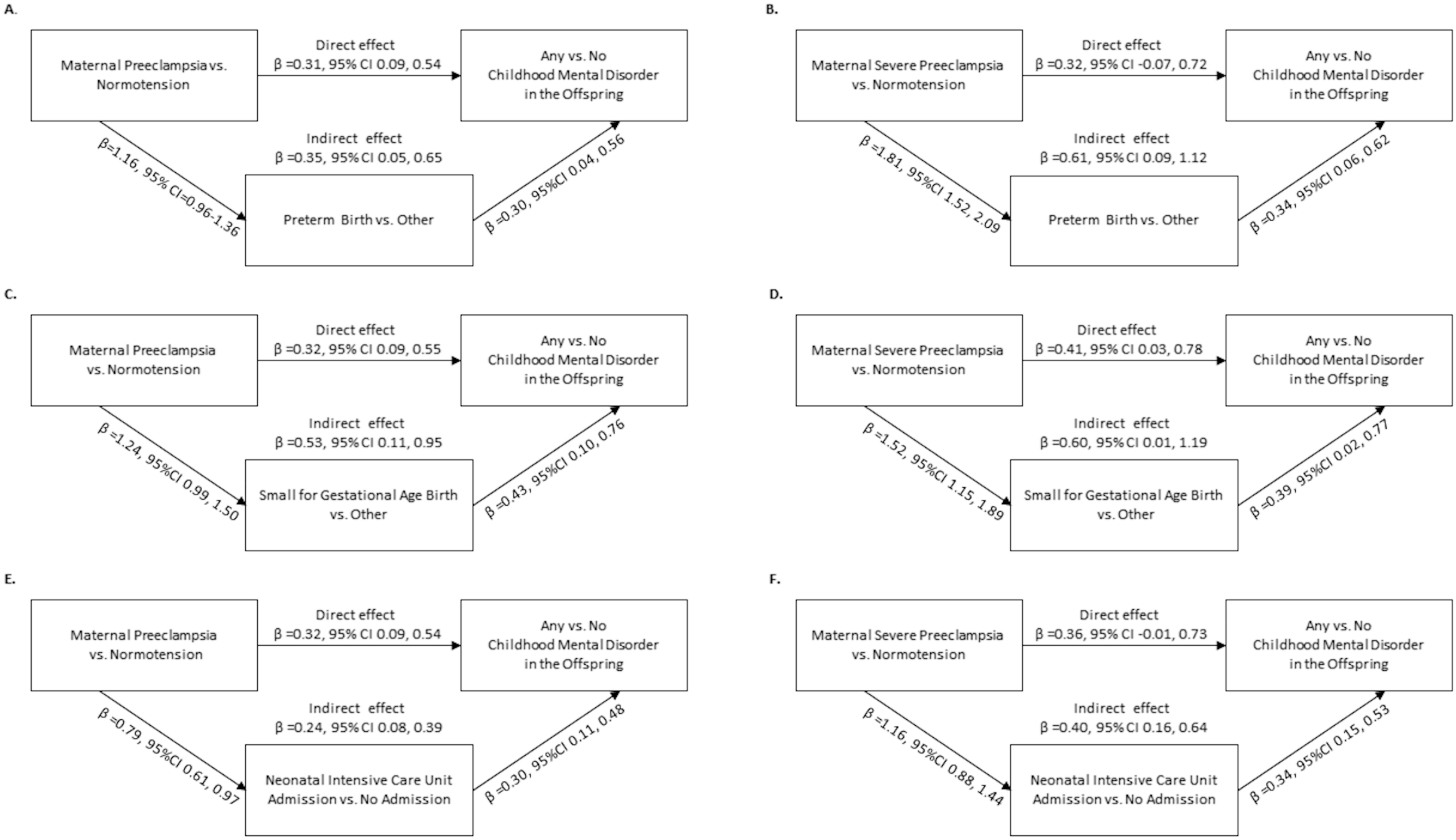
0	2285	2276	2269	2256	2236	2212	2198	2045	1242	177	2
1	1161	1159	1157	1151	1133	1117	1095	1024	649	135	11
2	461	459	455	447	436	428	425	404	261	72	19
3	139	139	139	138	133	129	124	119	84	30	11

C.



Number at Risk

0	2267	2255	2249	2240	2233	2226	2208	2055	1244	177	2
1	1145	1139	1138	1136	1133	1123	1108	1033	655	135	11
2	443	439	438	438	436	435	431	406	261	72	19
3	138	137	137	137	135	131	128	120	83	30	11


A.
Maternal Preeclampsia vs. Normotension
Direct effect
β =0.31, 95% CI 0.09, 0.54
Any vs. No Childhood Mental Disorder in the Offspring
β=1.16, 95% CI=0.96-1.36
Indirect effect
β =0.35, 95% CI 0.05, 0.65
Preterm Birth vs. Other
β =0.30, 95%CI 0.04, 0.56
B.
Maternal Severe Preeclampsia vs. Normotension
Direct effect
β =0.32, 95% CI -0.07, 0.72
Any vs. No Childhood Mental Disorder in the Offspring
β =1.81, 95%CI 1.52, 2.09
Indirect effect
β =0.61, 95% CI 0.09, 1.12
Preterm Birth vs. Other
β =0.34, 95%CI 0.06, 0.62
C.
Maternal Preeclampsia vs. Normotension
Direct effect
β =0.32, 95% CI 0.09, 0.55
Any vs. No Childhood Mental Disorder in the Offspring
β =1.24, 95%CI 0.99, 1.50
Indirect effect
β =0.53, 95% CI 0.11, 0.95
Small for Gestational Age Birth vs. Other
β =0.43, 95%CI 0.10, 0.76
D.
Maternal Severe Preeclampsia vs. Normotension
Direct effect
β =0.41, 95% CI 0.03, 0.78
Any vs. No Childhood Mental Disorder in the Offspring
β =1.52, 95%CI 1.15, 1.89
Indirect effect
β =0.60, 95% CI 0.01, 1.19
Small for Gestational Age Birth vs. Other
β =0.39, 95%CI 0.02, 0.77
E.
Maternal Preeclampsia vs. Normotension
Direct effect
β =0.32, 95% CI 0.09, 0.54
Any vs. No Childhood Mental Disorder in the Offspring
β =0.79, 95%CI 0.61, 0.97
Indirect effect
β =0.24, 95% CI 0.08, 0.39
Neonatal Intensive Care Unit Admission vs. No Admission
β =0.30, 95%CI 0.11, 0.48
F.
Maternal Severe Preeclampsia vs. Normotension
Direct effect
β =0.36, 95% CI -0.01, 0.73
Any vs. No Childhood Mental Disorder in the Offspring
β =1.16, 95%CI 0.88, 1.44
Indirect effect
β =0.40, 95% CI 0.16, 0.64
Neonatal Intensive Care Unit Admission vs. No Admission
β =0.34, 95%CI 0.15, 0.53

DATA SUPPLEMENT

MATERNAL HYPERTENSIVE PREGNANCY DISORDERS AND MENTAL DISORDERS IN CHILDREN

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Table S1. The Diagnostic Classification And Incidence of Maternal Hypertensive Pregnancy Disorders.

Hypertensive Disorder	Who Is Included?	Diagnostic Criteria	ICD-codes	Number of cases (%)
Normotension	Normotensive women with no diagnosis of chronic hypertension by childbirth and no diagnosis of hypertensive pregnancy disorders in previous or current pregnancy.	-	-	3734(78.7%)
Hypertension Only Before Current Pregnancy	Women diagnosed either with hypertensive pregnancy disorders in previous pregnancies or with chronic hypertension only before the current pregnancy started. These women had no hypertensive disorder diagnosis in the current pregnancy.	Has fulfilled the criteria for any of the specific disorders listed below, but only before the current pregnancy.	ICD-9: 642, 401-405; ICD-10: I1, O10-O11, O13-O16:	333(7.7%)
Unspecified Hypertension in Current Pregnancy	Women diagnosed with unspecified hypertension in current pregnancy.	Transient hypertension during current pregnancy.	ICD-10:O16	4(0.1%)
Chronic Hypertension in Current Pregnancy	Women diagnosed with chronic hypertension during the current pregnancy.	Blood pressure ≥140/90 mmHg SBP/DBP present from pre-pregnancy or before 20 gestational weeks onwards.	ICD-10:O10, I10	200(4.2%)
Gestational Hypertension in Current Pregnancy	Women diagnosed with gestational hypertension in the current pregnancy.	Newly elevated blood pressure (≥140/90 mmHg SBP/DBP) at ≥20 gestational weeks without proteinuria.	ICD-10:O13	263(5.5%)
Preeclampsia in Current Pregnancy	Women diagnosed with preeclampsia, superimposed preeclampsia, eclampsia or HELLP syndrome in the current pregnancy	Newly elevated blood pressure (≥140 mmHg SBP and/or ≥90 mmHg DBP) at ≥20 gestational weeks combined with proteinuria (urinary excretion of ≥0.3 g protein in a 24-hour specimen or at least ++ in one or more or + dipstick in two consecutive measurements).	ICD-10:O11, O14, O15	209(4.4%)
Mild /Moderate Preeclampsia in Current Pregnancy	Women diagnosed with mild/moderate preeclampsia in current pregnancy.	Completes the criteria of preeclampsia but not severe preeclampsia.	ICD-10:O14.0	122(2.6%)
Severe Preeclampsia in Current Pregnancy	Women diagnosed with severe preeclampsia in current pregnancy.	SBP≥160 mmHg, DBP≥110 mmHg, and/or ≥5g proteinuria in a 24-h urine collection.	ICD-10:O14.1	63(1.3%)

ICD=International Classification of Diseases. SBP=systolic blood pressure. DBP=diastolic blood pressure. HELLP= hemolysis, elevated liver enzymes, and low platelets.

Table S2. The diagnostic concordance of maternal hypertensive pregnancy disorder diagnoses in the current pregnancy in the Finnish Care Register for Health Care (HILMO) and Medical Birth Register (MBR) with diagnoses verified by a clinical jury of two clinicians and a nurse. Kappa-coefficient=0.66 and Gwet's AC1 coefficient=0.79 both suggest substantial agreement of diagnoses in the medical registers with the jury-verified diagnoses.

Jury-Verified Diagnoses	Normotension (n=544)	Chronic Hypertension in Current Pregnancy (n=160)	Gestational Hypertension in Current Pregnancy (n=79)	Preeclampsia in Current Pregnancy (n=71)
Diagnoses in HILMO or MBR	N(%)	N(%)	N(%)	N(%)
Normotension (n=599)	**528(97.1%)**	36(22.5%)	30(38.0%)	5(7.0%)
Chronic Hypertension in Current Pregnancy (n=101)	2(0.4%)	**90(56.3%)**	5(6.3%)	4(5.6%)
Gestational Hypertension in Current Pregnancy (n=64)	5(0.9%)	15(9.4%)	**35(44.3%)**	9(12.7%)
Preeclampsia in Current Pregnancy (n=90)	9(1.7%)	19(11.9%)	9(11.4%)	**53(74.6%)**

The table shows the number and percentage of women in each jury-verified diagnostic category based on the Medical Birth Register (MBR) and Care Register for Health Care (HILMO) diagnostic groups. Women with unspecified hypertensive disorder in the current pregnancy in the HILMO or MBR and women with hypertensive disorders only before current pregnancy in case reports, HILMO or MBR were excluded from these analysis.

Table S3. **Mental Disorders in the Offspring.** The number and percentage of offspring with different mental disorders and the median (mdn) age (in years) at the time of first diagnosis and its interquartile range (IQR) in the total sample and in the hypertensive disorder groups and the International Classification of Diseases, Ninth (ICD-9) and Tenth Revision (ICD-10) diagnostic codes used to identify the different diagnoses.

Maternal Hypertensive Disorder Group			Normotension	Hypertension Only Before Current Pregnancy	Unspecified Hypertension in Current Pregnancy	Chronic Hypertension in Current Pregnancy	Gestational Hypertension in Current Pregnancy	Preeclampsia in Current Pregnancy	Mild /Moderate Preeclampsia in Current Pregnancy	Severe Preeclampsia in Current Pregnancy
		N (%)	3734(78.7%)	333(7.7%)	4(0.1%)	200(4.2%)	263(5.5%)	209(4.4%)	122(2.6%)	63(1.3%)
Diagnostic Outcome in the Offspring	ICD-10	N (%) / Mdn (IQR), y*	N (%) / Mdn (IQR), y*	N (%)/ Mdn (IQR), y*	N (%) / Mdn (IQR), y*	N (%) / Mdn (IQR), y*	N (%) / Mdn (IQR), y*	N (%) / Mdn (IQR), y*	N (%) / Mdn (IQR), y*	N (%) / Mdn (IQR), y*
Any Childhood Mental Disorder	F00-F99	412(8.7%)/ 4.9(3.4-6.4)	300(8.0%)/ 5.0(3.4-6.4)	21(6.3%)/ 4.9(3.5-6.4)	1(25.0%)/ NA†	26 (13.0%)/ 4.4(3.4-6.3)	33(12.5%)/ 4.4(3.0-6.5)	31(14.8%)/ 4.8(2.9-6.2)	16(13.1%)/ 5.0(4.1-5.9)	11(17.5%)/ 4.8(2.7-6.9)
Non-Affective Psychosis	F2	2(0.04%)/ NA†	2(0.1%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†
Mood Disorders	F3	4(0.1%)/ 7.4(6.9-8.2)	3(0.1%)/ NA†	0(0.0%) /NA†	0(0.0%)/ NA†	1 (0.5%)/ NA†	0(0.0%)/ NA†	0(0.0%) /NA†	0(0.0%)/ NA†	0(0.0%)/ NA†
Neurotic, Stress-Related, and Somatoform Disorders	F4	12(0.3%)/ 6.2(5.0-7.6)	11(0.3%)/ 6.5(4.8-7.7)	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	1(0.4%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†
Behavioural syndromes associated with physiological disturbances and physical factors	F5	33 (0.7%)/ 2.8(0.8-5.9)	27(0.7%)/ 4.0(1.6-6.2)	1(0.3%)/ NA†	0(0.0%)/ NA†	2(1.0%)/ NA†	2(0.8%)/ NA†	1(0.5%)/ NA†	1(0.8%)/ NA†	0(0.0%)/ NA†
Disorders of Adult Personality and Behavior	F6	2(0.04%)/ NA†	2(0.1%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†
Mental Retardation	F7	19(0.4%)/ 4.3(3.9-6.2)	16(0.4%)/ 5.7(3.9-6.2)	1(0.3%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	1(0.4%)/ NA†	1(0.5%)/ NA†	0(0.0%) /NA†	1(1.6%)/ NA†
Psychological Development Disorders	F8	256(5.4%)/ 4.7(3.4-6.0)	179(4.8%)/ 4.7(3.5-6.0)	14(4.2%)/ 4.7(3.6-5.9)	1(25.0%)/ NA	19(9.5%)/ 4.3(3.5-5.9)	22(8.4%)/ 4.2(3.0-6.0)	21(10.0%)/ 4.6(2.9-6.8)	11(9.0%)/ 5.2(4.0-6.6)	7(11.1%)/ 4.8(2.8-7.5)
Behavioral and Emotional Disorders	F90-F98	200(4.2%)/ 6.1(4.8-7.1)	150(4.0%)/ 6.1(4.9-7.2)	7(2.1%)/ 6.4(4.3-6.9)	0(0.0%)/ NA	12(6.0%)/ 6.2(4.9-6.6)	13(4.9%)/ 6.4(0.4-7.0)	18(8.6%)/ 5.7(4.8-6.8)	10(8.2%)/ 5.7(5.1-6.7)	7(11.1%)/ 5.1(1.0-6.9)
Unspecified Mental Disorder	F99	1(0.02%)/ NA†	1(0.03%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†	0(0.0%)/ NA†

*Mdn=median; IQR= interquartile range; y=years. †NA=Not available.
For cells with less than 4 participants, no median age or IQR is given to protect participant anonymity and since IQR could not be calculated in these groups.

Table S4. The Sample Characteristics and Associations between Covariates and Maternal Hypertensive Disorders. Means and standard deviations in hypertensive disorder groups for continuous covariates and number and percentage of participants with hypertensive disorders for categorical covariates. Median ages at first diagnosis and its interquartile ranges for diagnostic entities. P-values from chi-squared, Kruskal-Wallis and ANOVA-tests.

Maternal Hypertensive Disorder **Characteristic**	**Normotension**	**Hypertension Before Current Pregnancy**	**Unspecified Hypertension in Current Pregnancy**	**Chronic Hypertension in Current Pregnancy**	**Gestational Hypertension in Current Pregnancy**	**Preeclampsia in Current Pregnancy**	
N(%)	3734(78.7%)	333(7.0%)	4(0.1%)	200(4.2%)	263(5.5%)	209(4.4%)	
Maternal Characteristics	Mean(SD)*/ N(%)	Mean(SD)*/ N(%)	Mean(SD)*/ N(%)	Mean(SD)*/ N(%)	Mean(SD)*/ N(%)	Mean(SD)*/ N(%)	p
Age at Delivery (years)	31.2(4.8)	32.2(4.5)	33.7(3.2)	34.4(5.1)	32.2 (5.2)	31.5 (5.1)	<.001
Education Level							
Primary or Secondary	1376(40.2%)	123(40.5%)	2(50.0%)	97(50.5%)	114(45.6%)	76(39.4%)	
Lover Tertiary	871(25.5%)	85(28.0%)	1(25.0%)	42(21.9%)	73(29.2%)	61(31.6%)	.02
Upper Tertiary	1172(34.3%)	96(31.6%)	1(25.0%)	53(27.6%)	63(25.2%)	56(29.0%)	
Data Missing	315(8.4%)	29(8.7%)	0(0.0%)	8(4.0%)	13(4.9%)	16(7.7%)	.04
Parity							
Primiparous	1542(41.3%)	6(1.8%)	3(75.0%)	78(39.0%)	116(44.9%)	97(46.4%)	<.001
Multiparous	2192(58.7%)	327(98.2%)	1(25.0%)	122(61.0%)	147(55.1%)	112(53.6%)	
Alcohol Use during Pregnancy							
Yes	437(15.7%)	35(14.6%)	3(100.0%)	30(17.6%)	31(15.3%)	166(10.5%)	.51
No	2344(84.3%)	205(85.4%)	0(0.0%)	140(82.4%)	171(84.7%)	13(89.5%)	
Data Missing	953(25.5%)	93(27.9%)	1(25.0%)	30(15.0%)	61(23.2%)	57(27.3%)	.02
Smoking During Pregnancy							
Did Not Smoke	3389(91.2%)	309(93.4%)	4(100.0%)	186(93.5%)	240(91.3%)	191(91.8%)	
Quit during 1st Trimester	128(3.4%)	11(3.3%)	0(0.0%)	6(3.0%)	7(2.7%)	10(4.8%)	.69
Smoked Throughout	197(5.3%)	11(3.3%)	0(0.0%)	7(3.5%)	16(6.1%)	7(3.4%)	
Data Missing	20(0.5%)	2(0.6%)	0(0.0%)	1(0.5%)	0(0.0%)	1(0.5%)	.91
Early Pregnancy Body Mass Index [weight (kilograms) / height (meters)^2]							
Continuous	23.9(4.5)	25.3(5.8)	26.3(5.9)	29.4(6.4)	26.4(5.8)	26.8(6.4)	<.001
Underweight	141(3.8%)	7(2.1%)	0(0.0%)	1(0.5%)	5(1.9%)	5(2.4%)	
Normal Weight	2504(67.1%)	193(58.0%)	2(50.0%)	61(30.5%)	135(51.3%)	93(44.5%)	<.001
Overweight	694(18.6%)	80(24.0%)	1(25.0%)	46(23.0%)	51(19.4%)	57(27.3%)	
Obese	395(10.6%)	53(15.9%)	1(25.0%)	92(46.0%)	72(27.4%)	54(25.8%)	

Diabetes							
No diabetes	3301(88.4%)	257(77.2%)	3(75.0%)	115(57.5%)	197(74.9%)	156(74.6%)	<.001
Diabetes in Previous Pregnancy	53(1.4%)	16(4.8%)	0(0.0%)	5(2.5%)	11(4.2%)	6(2.9%)	
Diabetes in Current Pregnancy	380(10.2%)	60(18.0%)	1(25.0%)	80(40.0%)	55(20.9%)	47(22.5%)	
Systolic Blood Pressure (mm/hg)	126.5(11.0)	131.9(12.3)	139.5(2.1)	153.2(16.3)	150.4(14.0)	168.2(19.5)	<.001
Data Missing	3226(86.4%)	183(55.0%)	2(50.0%)	39(19.5%)	155(58.9%)	111(53.1%)	<.001
Diastolic Blood Pressure (mm/hg)	81.9(8.0)	85.5(7.2)	90.0(7.1)	100.6(9.2)	99.3(7.7)	104.7(10.6)	<.001
Data missing	3226(86.4%)	183(55.0%)	2(50.0%)	39(19.5%)	155(58.9%)	111(53.1%)	<.001
Lifetime Diagnosis of Any Mental Disorder							
No	3113(83.4%)	275(82.6%)	4(100.0%)	169(84.5%)	221(84.0%)	172(82.3%)	.93
Yes	621(16.6%)	58(17.4%)	0(0.0%)	31(15.5%)	42(16.0%)	37(17.7%)	
Median age at first diagnosis (IQR†)	27.7(20.0-34.0)	30.0(21.5-34.3)	NA‡	33.4(27.2-39.4)	27.2(19.2-36.1)	27.1(18.4-35.7)	.04
Paternal Characteristics							
Lifetime Diagnosis of Any Mental Disorder							
No	1721(92.6%)	164(94.8%)	2(100.0%)	105(96.3%)	133(95.0%)	92(90.2%)	.37
Yes	138(7.4%)	9(5.2%)	0(0.0%)	4(3.7%)	7(5.0%)	10(9.8%)	
Data missing	1875(50.2%)	160(48.0%)	2(50.0%)	91(45.5%)	123(46.8%)	107(51.2%)	.66
Median age at first diagnosis (IQR†)	27.1(20.2-34.9)	28.7(21.8-35.2)	NA‡	28.7(21.8-35.2)	20.5(13.9-38.3)	22.5(19.1-31.7)	.18
Lifetime Diagnosis of Any Hypertensive Disorder							
No	1826(98.2%)	169(97.7%)	2(100.0%)	107(98.2%)	134(95.7%)	100(98.0%)	.49
Yes	33(1.8%)	4(2.3%)	0(0.0%)	2(1.8%)	6(4.3%)	2(2.0%)	
Data missing	1875(50.2%)	160(48.0%)	2(50.0%)	91(45.5%)	123(46.8%)	107(51.2%)	.66
Median age at first diagnosis (IQR†)	40.6(34.1-44.5)	36.4(32.3-39.6)	NA‡	NA‡	20.5(13.9-38.3)	NA‡	.22
Child Characteristics							
Birth Year	2008.4(0.7)	2008.1(0.9)	2008.0(0.8)	2008.0(0.9)	2008.2(0.9)	2008.2(0.9)	<001
2006	18(0.5%)	18(5.4%)	0(0.0%)	14(7.0%)	12(4.6%)	8(3.8%)	
2007	332(8.9%)	47(14.1%)	1(25.0%)	34(17.0%)	40(15.2%)	30(14.4%)	
2008	1821(48.8%)	162(48.6%)	2(50.0%)	98(49.0%)	118(44.9%)	94(45.0%)	<.001
2009	1342(35.9%)	97(29.1%)	1(25.0%)	53(26.5%)	81(30.8%)	70(33.5%)	
2010	221(5.9%)	9(2.7%)	0(0.0%)	1(0.5%)	12(4.6%)	7(3.3%)	
Sex							
Girl	1800(48.2%)	160(48.0%)	1(25.0%)	85(42.5%)	120(45.6%)	101(48.3%)	.47
Boy	1934(51.8%)	173(52.0%)	3(75.0%)	115(57.5%)	143(54.4%)	108(51.7%)	

Gestational Age (weeks)	40.0(1.5)	39.7(1.5)	40.1(1.0)	39.6(1.6)	39.9(1.7)	38.3(2.8)	<.001
Preterm Birth	113(3.0%)	12(3.6%)	0(0.0%)	8(4.0%)	11(4.2%)	45(21.5%)	<.001
Other (≥37) weeks)	3617(97.0%)	321(96.4%)	4(100.0%)	192(96.0%)	252(95.8%)	164(78.5%)	
Data Missing	4(0.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	.96
Birth Weight Adjusted for Sex and Gestational Age							
SD score	-0.04(0.95)	0.14(0.94)	-0.05(0.21)	-0.19(1.03)	-0.16(1.11)	-0.54(1.27)	<.001
Small for gestational age	52(1.4%)	5(1.5%)	0(0.0%)	9(4.5%)	12(4.6%)	27(12.9%)	<.001
Other	3675(98.6%)	327(98.5%)	4(100.0%)	191(95.5%)	251(95.4%)	182(87.1%)	
Data Missing	7(0.2%)	1(0.3%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	.91
Neonatal Intensive Care Unit Admission							
Yes	286(7.7%)	26(7.8%)	0(0.0%)	30(15.6%)	31(11.8%)	55(26.3%)	<.001
No	3438(92.3%)	307(92.2%)	4(100.0%)	162(84.4%)	232(88.2%)	154(77.7%)	
Data Missing	10(0.3%)	0(0.0%)	0(0.0%)	8(4.0%)	0(0%)	0(0.0%)	<.001

SD*=standard deviation. †IQR=Interquartile Range. ‡NA=Not available.

Table S5. The Associations of the Covariates with the Hazard of Any Childhood Mental Disorder in the Offspring. Hazard Ratios and 95% Confidence Intervals from Unadjusted Cox Proportional Hazards Models.

	Any Childhood Mental Disorder in the Offspring	
Characteristic	HR(95 % CI)*	p
Maternal Characteristics		
Age at Delivery	0.98(0.96-1.00)	.11
Education:		
Primary or Secondary vs. Lower Tertiary	1.37(1.07-1.75)	.01
Primary or Secondary vs. Upper Tertiary	2.03(1.57-2.63)	<.001
Lower Tertiary vs. Upper Tertiary	1.49(1.11-2.00)	.01
Body Mass Index in Early Pregnancy	1.05(1.04-1.07)	<.001
Underweight vs. normal weight	1.22(0.70-2.14)	.49
Overweight vs. normal weight	1.56(1.23-1.99)	<.001
Obese vs. normal weight	2.32(1.83-2.95)	<.001
Parity: Primiparous vs. Multiparous	1.15(0.94-1.40)	.16
Lifetime Diagnosis of Any Mental Disorder (yes vs. no)	2.10(1.70-2.60)	<.001
Alcohol Use During Pregnancy (yes vs. no)	0.79(0.57-1.09)	.15
Smoking During Pregnancy		
Quit during 1st trimester vs. no smoking	1.20(0.72-1.97)	.49
Smoked throughout pregnancy vs. no smoking	1.88(1.34-2.65)	<.001
Smoked throughout vs. quit during 1st trimester	1.58(0.87-2.84)	.13
Diabetes Disorders		
Diabetes in Previous Pregnancy vs. no diabetes	1.12(0.55-2.25)	.76
Diabetes in Current Pregnancy vs. no diabetes	1.84(1.45-2.33)	<.001
Paternal Characteristics		
Lifetime Diagnosis of Any Mental Disorder (yes vs. no)	1.99(1.26-3.15)	.003
Lifetime Diagnosis of Any Hypertensive Disorder (yes vs. no)	1.23(0.46-3.32)	.68
Child Characteristics		
Sex (Boys vs. Girls)	2.10(1.71-2.59)	<.001
Gestational age	0.95(0.90-1.01)	.09
Preterm vs. Other	1.70(1.15-2.52)	.01
Birthweight Adjusted for Gestation Length and Sex	0.98(0.89-1.08)	.68
Small for Gestational Age vs. Other	1.69(1.01-2.83)	.05
Neonatal Intensive Care Unit Admission vs. No Admission	1.60(1.21-2.12)	.001
Birth Year	0.93(0.82-1.06)	.29

*HR= Hazard Ratio; 95%CI= 95% Confidence Interval.

Table S6. Sensitivity Analyses of Maternal Hypertensive Disorders, Blood Pressure and Adverse Pregnancy Conditions and the Hazard of Childhood Mental Disorders in the Offspring. Mothers with Coronary Heart Disease or Stroke by Childbirth or Genitourinary Infections during Pregnancy Were Excluded.

	Offspring Mental Disorders					
	Any Childhood Mental Disorder		Psychological Development Disorders		Behavioral and Emotional Disorders	
	HR(95 % CI)*	p	HR(95% CI)*	p	HR(95% CI)*	p
Maternal Hypertension Before Current Pregnancy vs. Normotension	0.77(0.49-1.20)	.25	0.86(0.50-1.49)	.60	0.50(0.24-1.08)	.08
Maternal Unspecified Hypertension in Current Pregnancy vs. Normotension	3.40(0.48-24.21)	.22	5.74(0.80-40.98)	.08	0(NA)*	.96
Maternal Chronic Hypertension in Current Pregnancy vs. Normotension	1.51(1.00-2.28)	.05	1.84(1.12-2.99)	.02	1.42(0.78-2.57)	.25
Maternal Gestational Hypertension in Current Pregnancy vs. Normotension	1.49(1.04-2.15)	.03	1.66(1.05-2.61)	.03	1.21(0.68-2.13)	.52
Maternal Preeclampsia in Current Pregnancy vs. Normotension	1.91(1.32-2.76)	.001	2.18(1.39-3.44)	.001	2.21(1.35-3.62)	.002
Maternal Mild/Moderate Preeclampsia in Current Pregnancy vs. Normotension	1.66(1.00-2.75)	.05	1.90(1.03-3.50)	.04	2.09(1.10-3.97)	.02
Maternal Severe Preeclampsia in Current Pregnancy vs. Normotension	2.25(1.23-4.13)	.01	2.41(1.12-5.17)	.02	2.94(1.37-6.33)	.01
Maternal Systolic Blood Pressure during Current Pregnancy†‡	1.19(1.00-1.42)	.05	1.26(1.01-1.58)	.04	1.18(0.92-1.52)	.18
Maternal Diastolic Blood Pressure during Current Pregnancy †‡	1.13(0.94-1.35)	.19	1.16(0.92-1.46)	.22	1.06(0.82-1.38)	.64
Number of Maternal Adverse Pregnancy Conditions§						
1 vs. 0	1.50(1.17-1.91)	.001	1.50(1.10-2.05)	.01	1.43(1.01-2.03)	.05
2 vs. 0	2.09(1.56-2.80)	<.001	2.64(1.86-3.74)	<.001	2.03(1.33-3.10)	.001
3 vs. 0	3.22(2.20-4.72)	<.001	3.16(1.91-5.22)	<.001	3.85(2.31-6.42)	<.001

*HR=Hazard Ratio. 95%CI=95% Confidence Interval. NA=Not available.

All the analyses are stratified for offspring sex and adjusted for offspring birth year.

*Systolic blood pressure values were natural logarithm transformed to obtain normality.

†Both maternal systolic and diastolic blood pressure values during current pregnancy are expressed in standard deviation units to facilitate comparison of effect sizes.

§Maternal adverse pregnancy conditions are defined as overweight/obesity, diabetes and hypertensive disorders in pregnancy. Normal weight, normotensive women with no diabetes disorders are the reference group.

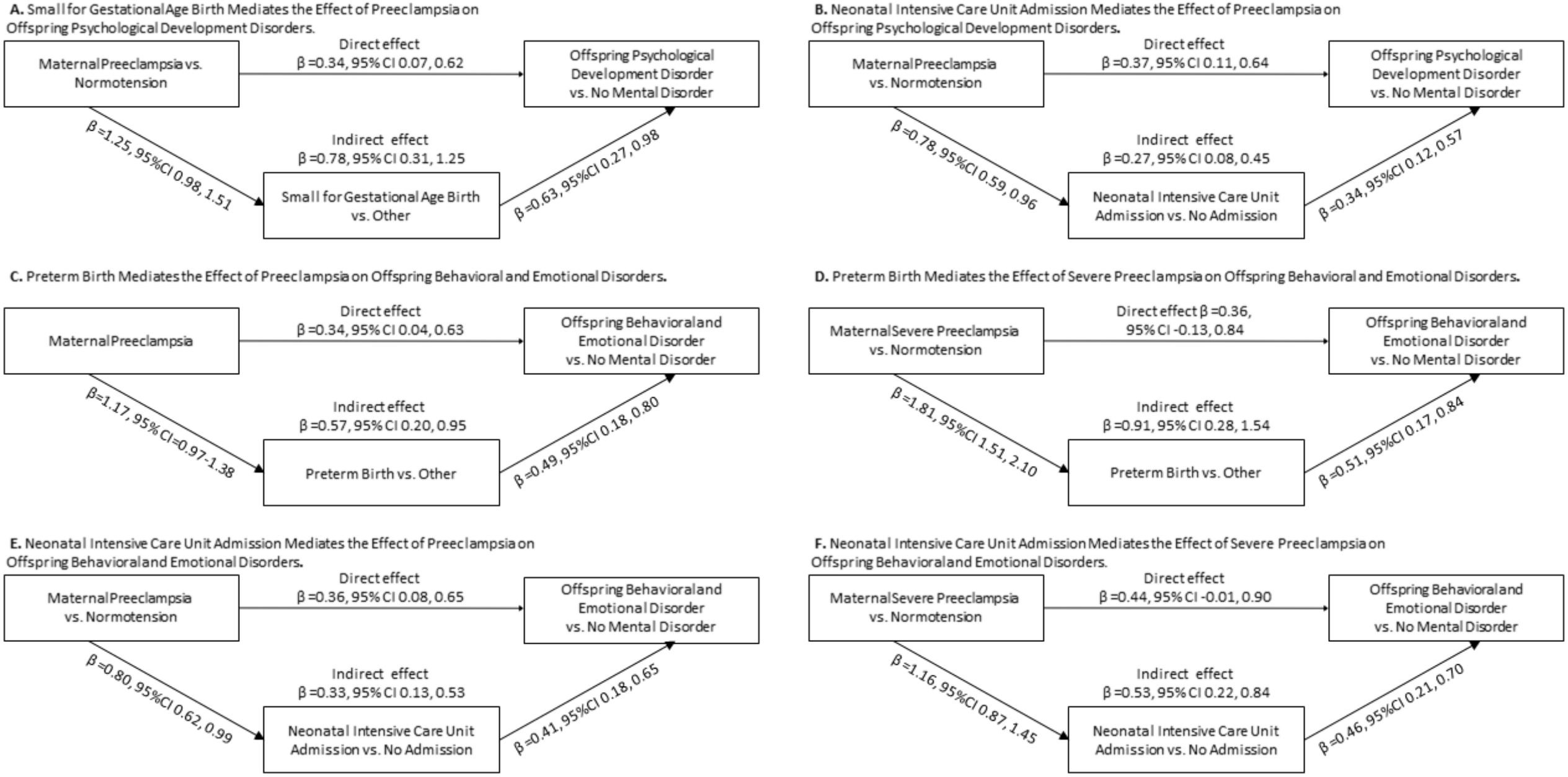

Figure S1. Mediation analyses on preterm and small for gestational age births and neonatal intensive care unit admission as mediators of the effects of maternal preeclampsia on offspring psychological development disorders (Panels A-B) and any and severe preeclampsia on offspring behavioral and emotional disorders (Panels C-F). Small for gestational age birth did not predict offspring behavioral and emotional disorders (p=.07), severe preeclampsia was not independently associated with offspring psychological development disorders (p=.054) and preterm birth did not predict offspring psychological development disorders when adjusting for maternal preeclampsia (p=.08). Hence, these mediation pathways were not tested. Standardized regression coefficients (β) and 95 % Confidence Intervals (CI) from logistic regressions and Sobel's Tests.